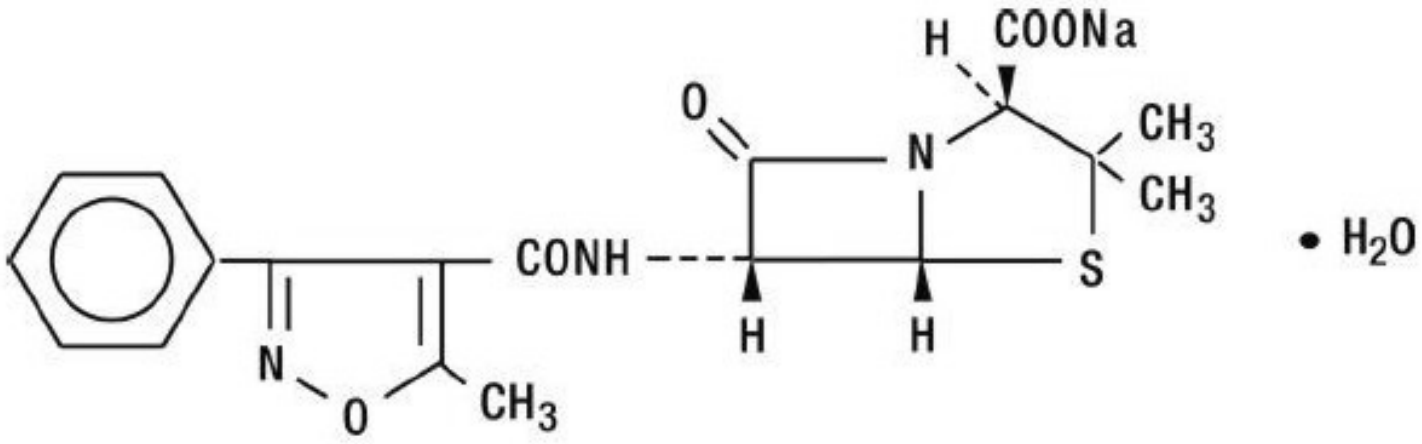
**OXACILLIN - oxacillin sodium injection, powder, for solution**
Sandoz Inc

**For Intramuscular or Intravenous Injection**
To reduce the development of drug-resistant bacteria and maintain the effectiveness of Oxacillin for Injection and other antibacterial drugs, Oxacillin for Injection should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

## DESCRIPTION
Oxacillin for Injection, USP is a semisynthetic antibiotic substance derived from 6-amino-penicillanic acid. It is the sodium salt in a parenteral dosage form. Each gram of Oxacillin Sodium contains approximately 2.5 mEq of sodium and is buffered with 20 mg dibasic sodium phosphate.

**OXACILLIN SODIUM**




$C_{19}H_{18}N_3NaO_5S \cdot H_2O$ MW=441.43

4-Thia-1-azabicyclo [3.2.0]heptane-2-carboxylic acid, 3,3-dimethyl-6-[[(5-methyl-3-phenyl-4-isoxazolyl) carbonyl] amino]-7-oxo-,monosodium salt, monohydrate, [2*S*(2α,5α,6β)].

## CLINICAL PHARMACOLOGY

**Microbiology**
Penicillinase-resistant penicillins exert a bactericidal action against penicillin-susceptible microorganisms during the state of active multiplication. All penicillins inhibit the biosynthesis of the bacterial cell wall.
The drugs in this class are highly resistant to inactivation by staphylococcal penicillinase and are active against penicillinase-producing and nonpenicillinase-producing strains of **Staphylococcus aureus.**
The penicillinase-resistant penicillins are active *in vitro* against a variety of other bacteria.

**Susceptibility Plate Testing**
Quantitative methods of susceptibility testing that require measurement of zone diameters or minimal inhibitory concentrations (MIC's) give the most precise estimates of antibiotic susceptibility. One such procedure has been recommended for use with discs to test susceptibility to this class of drugs. Interpretations correlate diameters on the disc test with MIC values. A penicillinase-resistant class disc may be used to determine microbial susceptibility to cloxacillin, dicloxacillin, methicillin, nafcillin, and oxacillin. With this procedure, employing a 5 microgram methicillin sodium disc, a report from the laboratory of "susceptible" (zone of at least 14 mm) indicates that the infecting organism is likely to respond to therapy. A report of "resistant" (zone of less than 10 mm) indicates that the infecting organism is not likely to respond to therapy. A report of "intermediate susceptibility" (zone of 10 to 13 mm) suggests that the organism might be susceptible if high doses of the antibiotic are used, or if the infection is confined to tissues and fluids (e.g. urine), in which high antibiotic levels are attained.
In general, all staphylococci should be tested against the penicillin G disc and against the methicillin disc. Routine methods of antibiotic susceptibility testing may fail to detect strains of organisms resistant to the penicillinase-resistant penicillins. For this reason, the use of large inocula and 48-hour incubation periods may be necessary to obtain accurate susceptibility studies with these antibiotics. Bacterial strains which are resistant to one of the penicillinase-resistant penicillins should be considered resistant to all of the drugs in the class.

**Pharmacokinetics**
Oxacillin Sodium, with normal doses, has insignificant concentrations in the cerebrospinal and ascitic fluids. It is found in therapeutic concentrations in the pleural, bile, and amniotic fluids. Oxacillin Sodium is rapidly excreted as unchanged drug in the urine by glomerular filtration and active tubular secretion.
Oxacillin Sodium binds to serum protein, mainly albumin. The degree of protein binding reported varies with the method of study and the investigator, but generally has been found to be 94.2 ± 2.1%.
Intramuscular injections give peak serum levels 30 minutes after injection. A 250 mg dose gives a level of 5.3 mcg/mL while a 500 mg dose peaks at 10.9 mcg/mL. Intravenous injection gives a peak about 5 minutes after the injection is completed. Slow IV dosing with 500 mg gives a 5 minute peak of 43 mcg/mL with a half-life of 20 to 30 minutes.

## INDICATIONS AND USAGE
The penicillinase-resistant penicillins are indicated in the treatment of infections caused by penicillinase-producing staphylococci which have demonstrated susceptibility to the drugs. Culture and susceptibility tests should be performed initially to determine the causative organism and their sensitivity to the drug (See **CLINICAL PHARMACOLOGY – Susceptibility Plate Testing**).
The penicillinase-resistant penicillins may be used to initiate therapy in suspected cases of resistant staphylococcal infections prior to the availability of laboratory test results. The penicillinase-resistant penicillins should not be used in infections caused by organisms susceptible to penicillin G. If the susceptibility tests indicate that the infection is due to an organism other than a resistant staphylococcus, therapy should not be continued with a penicillinase-resistant penicillin.
To reduce the development of drug-resistant bacteria and maintain the effectiveness of Oxacillin for Injection and other antibacterial drugs, Oxacillin for Injection should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

## CONTRAINDICATIONS
A history of a hypersensitivity (anaphylactic) reaction to any penicillin is a contraindication.

## WARNINGS
Serious and occasionally fatal hypersensitivity (anaphylactic shock with collapse) reactions have occurred in patients receiving penicillin. The incidence of anaphylactic shock in all penicillin-treated patients is between 0.015 and 0.04 percent. Anaphylactic shock resulting in death has occurred in approximately 0.002 percent of the patients treated. Although anaphylaxis is more frequent following a parenteral administration, it has occurred in patients receiving oral penicillins.
When penicillin therapy is indicated, it should be initiated only after a comprehensive patient drug and allergy history has been obtained. If an allergic reaction occurs, the drug should be discontinued and the patient should receive supportive treatment, e.g., artificial maintenance of ventilation, pressor amines, antihistamines, and corticosteroids. Individuals with a history of penicillin hypersensitivity may also experience allergic reactions when treated with a cephalosporin.
*Clostridium difficile* associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including oxacillin for injection, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.
*C. difficile* produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.
If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

## PRECAUTIONS

### General
Penicillinase-resistant penicillins should generally not be administered to patients with a history of sensitivity to any penicillin. Penicillin should be used with caution in individuals with histories of significant allergies and/or asthma. Whenever allergic reactions occur, penicillin should be withdrawn unless, in the opinion of the physician, the condition being treated is life-threatening and amenable only to penicillin therapy.
The oral route of administration should not be relied upon in patients with severe illness, or with nausea, vomiting, gastric dilation, cardiospasm, or intestinal hypermotility. Occasionally patients will not absorb therapeutic amounts of orally administered penicillin.
The use of antibiotics may result in overgrowth of nonsusceptible organisms. If new infections due to bacteria or fungi occur, the drug should be discontinued and appropriate measures taken.
Prescribing Oxacillin for Injection in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

**Information for Patients**
Patients should be counseled that antibacterial drugs including Oxacillin for Injection should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When Oxacillin for Injection is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may: (1) decrease the effectiveness of the immediate treatment, and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by Oxacillin for Injection or other antibacterial drugs in the future.
Diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

**Laboratory Tests**
Bacteriologic studies to determine the causative organisms and their susceptibility to the penicillinase-resistant penicillins should be performed (See **CLINICAL PHARMACOLOGY –- Microbiology**). In the treatment of suspected staphylococcal infections, therapy should be changed to another active agent if culture tests fail to demonstrate the presence of staphylococci.
Periodic assessment of organ system function including renal, hepatic, and hematopoietic should be made during prolonged therapy with the penicillinase-resistant penicillins.
Blood cultures, white blood cell, and differential cell counts should be obtained prior to initiation of therapy and at least weekly during therapy with penicillinase-resistant penicillins.
Periodic urinalysis, blood urea nitrogen, and creatinine determinations should be performed during therapy with the penicillinase-resistant penicillins and dosage alterations should be considered if these values become elevated. If any impairment of renal function is suspected or known to exist, a reduction in the total dosage should be considered and blood levels monitored to avoid possible neurotoxic reactions (See **DOSAGE AND ADMINISTRATION**).
SGOT and SGPT values should be obtained periodically during therapy to monitor for possible liver function abnormalities.

**Drug Interactions**
Tetracycline, a bacteriostatic antibiotic, may antagonize the bactericidal effect of penicillin and concurrent use of these drugs should be avoided.

**Carcinogenesis, Mutagenesis, Impairment of Fertility**
No long-term animal studies have been conducted with these drugs.
Studies on reproduction (nafcillin) in rats and rabbits reveal no fetal or maternal abnormalities before conception and continuously through weaning (one generation).

**Pregnancy Category B**
Reproduction studies performed in the mouse, rat, and rabbit have revealed no evidence of impaired fertility or harm to the fetus due to the penicillinase-resistant penicillins. Human experience with the penicillins during pregnancy has not shown any positive evidence of adverse effects on the fetus. There are, however, no adequate or well-controlled studies in pregnant women showing conclusively that harmful effects of these drugs on the fetus can be excluded. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

**Nursing Mothers**
Penicillins are excreted in breast milk. Caution should be exercised when penicillins are administered to a nursing woman.

**Pediatric Use**
Because of incompletely developed renal function in newborns, penicillinase-resistant penicillins (especially methicillin) may not be completely excreted, with abnormally high blood levels resulting. Frequent blood levels are advisable in this group with dosage adjustments when necessary. All newborns treated with penicillins should be monitored closely for clinical and laboratory evidence of toxic or adverse effects (See **DOSAGE AND ADMINISTRATION**).

**ADVERSE REACTIONS**

**Body as a Whole**
The reported incidence of allergic reactions to penicillin ranges from 0.7 to 10 percent (See **WARNINGS**). Sensitization is usually the result of treatment but some individuals have had immediate reactions to penicillin when first treated. In such cases, it is thought that the patients may have had prior exposure to the drug via trace amounts present in milk and vaccines.
Two types of allergic reactions to penicillin are noted clinically, immediate and delayed.
Immediate reactions usually occur within 20 minutes of administration and range in severity from urticaria and pruritus to angioneurotic edema, laryngospasm, bronchospasm, hypotension, vascular collapse, and death. Such immediate anaphylactic reactions are very rare (See **WARNINGS**) and usually occur after parenteral therapy but have occurred in patients receiving oral therapy.

Another type of immediate reaction, an accelerated reaction, may occur between 20 minutes and 48 hours after administration and may include urticaria, pruritus, and fever. Although laryngeal edema, laryngospasm, and hypotension occasionally occur, fatality is uncommon.
Delayed allergic reactions to penicillin therapy usually occur after 48 hours and sometimes as late as 2 to 4 weeks after initiation of therapy. Manifestations of this type of reaction include serum sickness-like symptoms (i.e., fever, malaise, urticaria, myalgia, arthralgia, abdominal pain) and various skin rashes. Nausea, vomiting, diarrhea, stomatitis, black or hairy tongue, and other symptoms of gastrointestinal irritation may occur, especially during oral penicillin therapy.

**Nervous System Reactions**
Neurotoxic reactions similar to those observed with penicillin G may occur with large intravenous doses of the penicillinase-resistant penicillins especially in patients with renal insufficiency.

**Urogenital Reactions**
Renal tubular damage and interstitial nephritis have been associated with the administration of methicillin sodium and infrequently with the administration of nafcillin and oxacillin. Manifestations of this reaction may include rash, fever, eosinophilia, hematuria, proteinuria, and renal insufficiency. Methicillin-induced nephropathy does not appear to be dose-related and is generally reversible upon prompt discontinuation of therapy.

**Gastrointestinal Reactions**
**Pseudomembranous colitis has been reported with the use of Oxacillin Sodium (and other broad spectrum antibiotics); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use.**
Treatment with broad spectrum antibiotics alters normal flora of the colon and may permit overgrowth of clostridia. Studies indicate a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis. Cholestyramine and colestipol resins have been shown to bind the toxin *in vitro*.
Mild cases of colitis may respond to drug discontinuance alone.
Moderate to severe cases should be managed with fluid, electrolyte and protein supplementation as indicated.
When the colitis is not relieved by drug discontinuance or when it is severe, oral vancomycin is the treatment of choice for antibiotic-associated pseudomembranous colitis produced by **C. difficile**. Other causes of colitis should also be considered.

**Metabolic Reactions**
Agranulocytosis, neutropenia, and bone marrow depression have been associated with the use of methicillin sodium, nafcillin, oxacillin, and cloxacillin. Hepatotoxicity, characterized by fever, nausea, and vomiting associated with abnormal liver function tests, mainly elevated SGOT levels, has been associated with the use of oxacillin and cloxacillin.

**DOSAGE AND ADMINISTRATION**
The penicillinase-resistant penicillins are available for oral administration and for intramuscular and intravenous injection. The sodium salts of methicillin, oxacillin, and nafcillin may be administered parenterally and the sodium salts of cloxacillin, dicloxacillin, oxacillin, and nafcillin are available for oral use.
Bacteriologic studies to determine the causative organisms and their sensitivity to the penicillinase-resistant penicillins should always be performed. Duration of therapy varies with the type and severity of infection as well as the overall condition of the patient, therefore it should be determined by the clinical and bacteriological response of the patient. In severe staphylococcal infections, therapy with penicillinase-resistant penicillins should be continued for at least 14 days. Therapy should be continued for at least 48 hours after the patient has become afebrile, asymptomatic, and cultures are negative. The treatment of endocarditis and osteomyelitis may require a longer term of therapy.
Concurrent administration of the penicillinase-resistant penicillins and probenecid increases and prolongs serum penicillin levels. Probenecid decreases the apparent volume of distribution and slows the rate of excretion by competitively inhibiting renal tubular secretion of penicillin. Penicillin-probenecid therapy is generally limited to those infections where very high serum levels of penicillin are necessary.
Oral preparations of the penicillinase-resistant penicillins should not be used as initial therapy in serious, life-threatening infections (See **PRECAUTIONS-General**). Oral therapy with the penicillinase-resistant penicillins may be used to follow-up the previous use of a parenteral agent as soon as the clinical condition warrants. For intramuscular gluteal injections, care should be taken to avoid sciatic nerve injury. With intravenous administration, particularly in elderly patients, care should be taken because of the possibility of thrombophlebitis.
RECOMMENDED DOSAGES FOR OXACILLIN FOR INJECTION, USP

| Drug | Adults | Infants and Children <40 kg (88 lbs) | Other Recommendations |
|---|---|---|---|
| Oxacillin | 250 to 500 mg IM or IV every 4 to 6 hours (mild to moderate infections) | 50 mg/kg/day IM or IV in equally divided doses every 6 hours (mild to moderate infections) | |

| | | | |
|---|---|---|---|
| | 1 gram IM or IV every 4 to 6 hours (severe infections) | 100 mg/kg/day IM or IV in equally divided doses every 4 to 6 hours (severe infections) | Premature and Neonates 25 mg/kg/day IM or IV |

**Directions for use**

For Intramuscular Use
Use Sterile Water for Injection, USP. Add 1.4 mL to the 250 mg vial, 2.7 mL to the 500 mg vial, 5.7 mL to the 1 gram vial, 11.5 mL to the 2 gram vial, and 23 mL to the 4 gram vial. Shake well until a clear solution is obtained. After reconstitution, vials will contain 250 mg of active drug per 1.5 mL of solution. The reconstituted solution is stable for 3 days at 70° F or for one week under refrigeration (40° F).

For Direct Intravenous Use
Use Sterile Water for Injection, USP or Sodium Chloride Injection, USP. Add 5 mL to the 250 mg and 500 mg vials, 10 mL to the 1 gram vial, 20 mL to the 2 gram vial, and 40 mL to the 4 gram vial. Withdraw the entire contents and administer slowly over a period of approximately 10 minutes.

For Administration by Intravenous Drip
Reconstitute as directed above (**For Direct Intravenous Use**) prior to diluting with Intravenous Solution.

STABILITY PERIODS FOR OXACILLIN FOR INJECTION, USP

| **Concentration mg/mL** | **Sterile $H_2O$ for Injection** | **Isotonic Sodium Chloride** | **M/6 Molar Sodium Lactate Solution** | **5% Dextrose in $H_2O$** | **5% Dextrose in 0.45% NaCl** | **10% Invert Sugar** | **Lactated Ringers Solution** |
|---|---|---|---|---|---|---|---|
| **ROOM TEMPERATURE (25°C)** | | | | | | | |
| 10-100 | 4 Days | 4 Days | | | | | |
| 10-30 | | | 24 Hrs | | 24 Hrs | | |
| 0.5-2 | | | | 6 Hrs | | 6 Hrs | 6 Hrs |
| **REFRIGERATION (4°C)** | | | | | | | |
| 10-100 | 7 Days | 7 Days | | | | | |
| 10-30 | | | 4 Days | 4 Days | 4 Days | 4 Days | 4 Days |
| **FROZEN (-15°C)** | | | | | | | |
| 50-100 | 30 Days | | | | | | |
| 250/1.5 mL | 30 Days | | | | | | |
| 100 | | 30 Days | | | | | |
| 10-100 | | | 30 Days | 30 Days | 30 Days | 30 Days | 30 Days |

Stability studies on Oxacillin Sodium at concentrations of 0.5 mg/mL and 2 mg/mL in various intravenous solutions listed below indicate the drug will lose less than 10% activity at room temperature (70° F) during a 6-hour period.

IV Solution
5% Dextrose in Normal Saline

10% D-Fructose in Water

10% D-Fructose in Normal Saline

Lactated Potassic Saline Injection

10% Invert Sugar in Normal Saline

10% Invert Sugar Plus 0.3% Potassium Chloride in Water

Travert 10% Electrolyte #1

Travert 10% Electrolyte #2

Travert 10% Electrolyte #3

Only those solutions listed above should be used for the intravenous infusion of Oxacillin Sodium. The concentration of the antibiotic should fall within the range specified. The drug concentration and the rate and volume of the infusion should be adjusted so that the total dose of oxacillin is administered before the drug loses its stability in the solution in use.

If another agent is used in conjunction with oxacillin therapy, **it should not be physically mixed** with oxacillin but should be administered separately.

Pharmacy Bulk Package
This glass vial contains 10 grams Oxacillin Sodium and is designed for use in the pharmacy in preparing IV additives. Add 93 mL Sterile Water for Injection, USP or Sodium Chloride Injection, USP. The resulting solution will contain 100 mg oxacillin sodium per mL.

Following reconstitution in this manner, the resulting solutions are stable for 4 days at room temperature or 7 days under refrigeration.

**CAUTION: NOT TO BE DISPENSED AS A UNIT.**

**HOW SUPPLIED**
Oxacillin for Injection, USP. Oxacillin sodium equivalent to 1, 2, or 10 grams oxacillin per vial.
NDC 0781-9109-95 1 gram vial packaged in 10s
NDC 0781-9111-95 2 grams vial packaged in 10s
NDC 0781-9113-95 10 grams Pharmacy Bulk Package packaged in 10s
Store dry powder at 20°-25°C (68°-77°F) [See USP Controlled Room Temperature].
10-2009
46022154
Manufactured in Austria by Sandoz GmbH
for Sandoz Inc., Princeton, NJ 08540

**1 GRAM VIAL LABEL**
OXAcillin
for Injection, USP
1 gram Rx only
Buffered -
for IM or IV use
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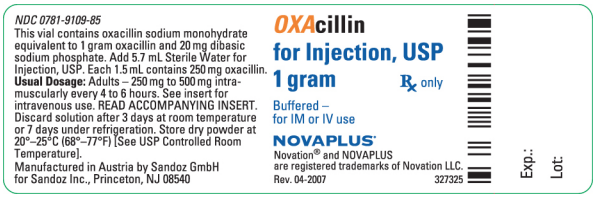
Rev. 04-2007 327325




**1 GRAM CASE LABEL**
Oxacillin for Injection, USP Rx only
1 gram
Case Qty.: 10 Vials
Manufactured in Austria by Sandoz GmbH
for Sandoz Inc., Princeton, NJ 08540

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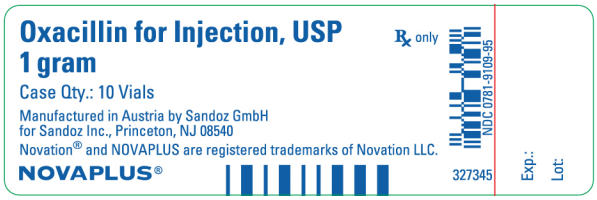


**2 GRAM VIAL LABEL**
OXAcillin
for Injection, USP
2 grams Rx only
Buffered -
for IM or IV use
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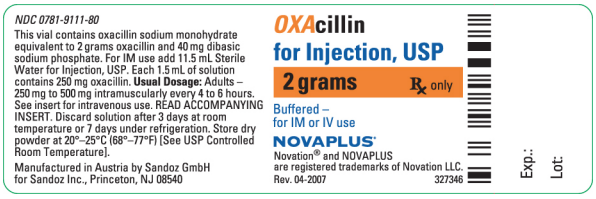


**2 GRAM CASE LABEL**
Oxacillin for Injection, USP Rx only
2 grams
Case Qty.: 10 Vials
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